PATENT SPECIFICATION (11) 1 554 275

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(21) Application No. 39054/76 (22) Filed 21 Sept. 1976
(31) Convention Application No. 12413/75
(32) Filed 24 Sept. 1975
(31) Convention Application No. 12414/75
(32) Filed 24 Sept. 1975
(31) Convention Application No. 7250/76
(32) Filed 9 June 1976 in
(33) Switzerland (CH)
(44) Complete Specification published 17 Oct. 1979
(51) INT CL² C07D 403/04 A61K 31/55 (C07D 403/04 243/38 295/12)
(52) Index at acceptance
C2C 1626 1747 200 213 215 220 227 22Y 246 247 250 252 25Y 28X 305 311 313 31Y 321 322 323 32Y 332 337 338 351 352 360 361 364 366 368 36Y 386 401 40Y 43X 453 45Y 620 621 623 624 625 628 630 652 65X 660 661 668 698 699 761 762 770 802 80Y LS LW TR WE ZB

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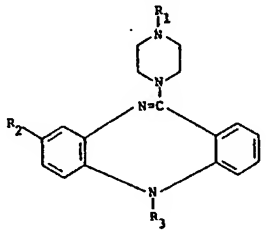
(54) DIBENZO[b,e][1,4]DIAZEPINES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to dibenzo[b,e]-[1,4]diazepines.

The present invention provides compounds of formula I,



I

wherein

R_1 is hydrogen, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, or alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof,

R_2 is fluorine or chlorine, and

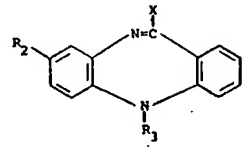
R_3 is alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof, or alkenyl of 3 or 4 carbon atoms, with the proviso that when R_3 is methyl, R_2 is fluorine.

Alkyl in R_1 has preferably 1 to 2 carbon atoms.

The alkoxy moiety in alkoxyalkyl or the hydroxy moiety in hydroxyalkyl is preferably located in the terminal position of the alkylene chain which preferably has 2 or 3, especially 2, carbon atoms. The alkoxy radical in alkoxyalkyl is preferably methoxy. The double bond in alkenyl is in the 2,3 or 3,4-position. Alkenyl is preferably allyl or 2-methyl-2-propenyl.

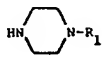
R_1 is preferably methyl. R_3 is preferably alkyl or alkoxyalkyl, especially alkyl. R_3 especially is methyl, ethyl or n-propyl.

The present invention also provides a process for the production of a compound of formula I as defined above, which comprises reacting a compound of formula II,



II

wherein
R_2 and R_3 are as defined above, and
X is a leaving group,
with a compound of formula III,



III

wherein
R_1 is as defined above.

The process may be effected in conventional manner for such reactions.

In the compound of formula II, X is attached by a covalent or ionic bond to the carbon atom, and signifies, for example, amino which may be substituted by one or two alkyl groups of 1 to 4 carbon atoms, especially 1 to 4 carbon atoms; sulfhydryl, alkoxy or alkylthio of 1 to 4 carbon atoms, for example methoxy or methylthio, p-nitrobenzylthio or tosyloxy, or preferably halogen, especially chlorine.

The process is conveniently effected at temperatures between 50° to 170°C in an inert organic solvent, for example xylene or dioxane.

The starting materials of formula II may be prepared in known manner, e.g. as described herein, for example via the corresponding lactam, e.g. by reaction with phosphorusoxychloride.

Free base forms of compounds of formula I may be converted into the acid addition salt forms in conventional manner and vice versa. A suitable acid is hydrochloric acid.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.

EXAMPLE 1

5-n-Propyl-8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine

5.74 g of 5-n-propyl-8-chloro-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-11-one, 30 ml of phosphorusoxychloride and 1 ml of N,N-dimethylaniline are boiled for 3 hours. The resulting solution of the imido-chloride of the lactam is evaporated to dryness, the residue evaporated twice more after the addition of xylene, and then boiled for 6 hours with 20 ml of dioxane and 25 ml of N-methylpiperazine. The resulting mixture is then concentrated as far as possible, and the residue is partitioned between aqueous ammonia and ether. The ethereal phase is washed with water, and extracted continuously with dilute acetic acid to remove the basic components. The base is set free by the addition of sodium hydroxide and taken up in chloroform. The chloroform phase is washed with water, dried over anhydrous sodium sulphate and concentrated to dryness. The residue is taken up in ether, filtered through basic aluminium oxide and crystallized from ether/petroleum ether to give the title compound; M.Pt. 120°—122°C.

The starting material may be obtained as follows:— 2-Nitro-4-chloro-diphenylamine-2'-carboxylic acid is converted via the acid chloride into 2-nitro-4-chloro-diphenylamine-2'-carboxylic acid methyl ester (M.Pt. 155°—156°). This is reacted with n-propyl iodide in the presence of sodium hydride in hexamethylphosphoric acid triamide to form N-n-propyl-2-nitro-4-chloro-diphenylamino-2'-carboxylic acid methyl ester. This is reduced in the presence of Raney nickel in ethyl acetate to form N-n-propyl-2-amino-4-chloro-diphenylamine-2'-carboxylic acid methyl ester. This is cyclized in the presence of sodium amide in boiling dioxane over several hours to yield the starting material used in Example 1.

In analogous manner to that described in Example 1, the following compounds of formula I may be obtained, wherein:—

Example	R_2	R_1	R_3	M.Pt.°
2	Cl	CH_3	C_2H_5	145—146°
3	Cl	CH_3	$CH_2CH_2OCH_3$	160—161°
4	F	CH_3	C_2H_5	133—135°
5	F	CH_3	n-C_3H_7	95—97° and 115—117°
6	F	CH_3	n-C_4H_9	124—125°
7	Cl	CH_3	CH_2—CH=CH_2	157—159°
8	Cl	CH_3	CH_2CH_2OH	157—159°

9	Cl	CH_3	iso-C_3H_7	152—154°
10	Cl	CH_3	iso-C_4H_9	128—131°
11	Cl	CH_3	n-C_4H_9	122—124°
12	F	CH_3	CH_3	172—174°
13	F	CH_2CH_2OH	CH_3	122—124°
14	F	C_2H_5	CH_3	146—147°
15	F	H	CH_3	147—149°
16	F	i-C_3H_7	CH_3	136—137°
17	F	n-C_3H_7	CH_3	136—138°
18	F	$CH_2CH_2OCH_3$	CH_3	107—109°
19	F	t-C_4H_9	CH_3	170—171°
20	F	CH_3	CH_2—CH=CH_2	139—140°

The compounds of formula I exhibit pharmacological activity. In particular, the compounds of formula I exhibit neuroleptic activity as indicated by standard tests. For example, the compounds inhibit spontaneous locomotor activity in mice upon administration of from 1 to 50 mg/kg p.o. animal body weight of the compounds according to the principles of Caviezel et al Pharm. Acta Helv. (1958) *33*, 469—484.

Additionally the compounds, wherein R_2 is chlorine and R_3 is alkyl or alkenyl, exhibit insignificant activity in tests indicating anti-chlolinergic activity, e.g. in the mydriasis test and in tests indicating effects on blood circulation, e.g. in the infusion test in the cat.

Therefore the compounds are indicated for use as neuroleptics and the compounds of formula I, wherein R_2 is chlorine and R_3 is alkyl or alkenyl, exhibit surprisingly beneficial activity than is expected for such compounds.

An indicated daily dose is from about 10 to 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 2 to about 250 mg of the compound, or in sustained release form.

Compounds of formula I, wherein R_2 is fluorine, additionally exhibit anti-depressant activity, as indicated in standard tests. For example, these compounds inhibit the ptosis and catalepsy produced by tetrabenazine on i.p. administration of from 0.1 to 10 mg/kg animal body weight of the compounds to rats.

These compounds are therefore further indicated for use as anti-depressants. An indicated daily dose is from about 5 to about 150 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 1 to about 35 mg of the compounds or in sustained release form.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be made in conventional manner so as to be, for example, a solution or a tablet.

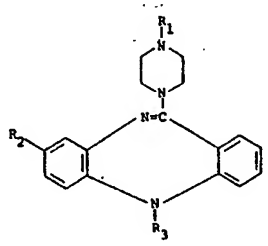
In one group of compounds R_1 is hydrogen, alkyl or hydroxyalkyl, and R_3 is hydroxyalkyl or alkoxyalkyl. In a sub-group R_3 is methoxyethyl, ethoxyethyl, propoxyethyl, ethoxypropyl, methoxypropyl or methoxybutyl.

In another group of compounds R_1 is alkyl and R_2 is chlorine, and R_3 is alkyl of 2 to 4 carbon atoms.

In another group of compounds R_2 is fluorine.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,



I

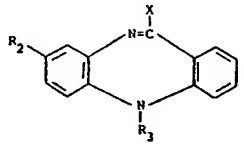
wherein

R_1 is hydrogen, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, or alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof,

R_2 is fluorine or chlorine, and

R_3 is alkyl of 1 to 4 carbon atoms, hydroxyalkyl or 2 to 4 carbon atoms, alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof, or alkenyl of 3 or 4 carbon atoms, with the proviso that when R_3 is methyl, R_2 is fluorine,

which comprises reacting a compound of formula II,



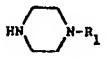
II

wherein

R_2 and R_3 are as defined above, and

X is a leaving group,

with a compound of formula III,



III

wherein

R_1 is as defined above.

2. A process for the production of a compound of formula I, as stated in Claim 1, substantially as hereinbefore described with reference to any one of the Examples.

3. A compound of formula I, whenever produced by a process according to Claim 1 or 2.

4. A compound of formula I, as defined in Claim 1.

5. A compound of Claim 4, wherein R_1 is hydrogen, alkyl or hydroxyalkyl, and R_3 is hydroxyalkyl or alkoxyalkyl.

6. A compound of Claim 4, wherein R_1 is alkyl, R_2 is chlorine and R_3 is alkyl of 2 to 4 carbon atoms.

7. A compound of Claim 4, wherein R_2 is fluorine.

8. A compound of Claim 4, which is 5-n-propyl-8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine.

9. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, Cl, C_2H_5.

10. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, Cl, $CH_2CH_2OCH_3$.

11. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, F, C_2H_5.

12. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, F, n-C_3H_7.

13. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, F, n-C_4H_9.

14. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, Cl, CH_2—CH=CH_2.

15. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, Cl, CH_2CH_2OH.

16. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, Cl, iso-C_3H_7.

17. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, Cl, iso-C_4H_9.

18. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, Cl, n-C_4H_9.

19. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, F, CH_3.

20. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_2CH_2OH, F, CH_3.

21. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively C_2H_5, F, CH_3.

22. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively H, F, CH_3.

23. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively i-C_3H_7, F, CH_3.

24. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively n-C_3H_7, F, CH_3.

25. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively $CH_2CH_2OCH_3$, F, CH_3.

26. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively t-C_4H_9, F, CH_3.

27. A compound of Claim 4, wherein R_1, R_2, R_3 are respectively CH_3, F, CH_2—CH=CH_2.

28. A compound according to any one of Claims 3 to 27 in free base form.

29. A compound according to any one of Claims 3 to 27 in acid addition salt form.

30. A pharmaceutical composition comprising a compound according to any one of Claims 3 to 27 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.